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A Case of Presumptive Monosomy 21 Re-Diagnosed as Unbalanced t(5p;21q) by FISH and Review of Literature

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By using fluorescence in situ hybridization (FISH), we demonstrate a case of monosomy 21 to result from an unbalanced translocation involving the short arm of chromosome 5 and the long arm of chromosome 21. Our case is compared to 3 similar cases of t(5p;21q) reported recently, which were also originally diagnosed as monosomy 21. The breakpoint on chromosome 5 in these cases occurred in the p13–p15 region, whereas the breakpoint on chromosome 21 was in the q21–q22 region. Comparison of the clinical findings in these patients demonstrated great similarities. Furthermore, a strong correlation between the clinical manifestations of these patients with cridu-chat syndrome patients was also noted. We suggest that cases with unbalanced t(5p;21q) represent a distinct syndrome which can be grouped under a new category of "5p/21q deletion syndrome." Am. J. Med. Genet. 70:174–178, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: monosomy 21; fluorescence in situ hybridization; 5p/21q deletion syndrome

INTRODUCTION

Monosomy 21 in liveborn infants is a very rare cytogenetic abnormality. Fewer than a dozen cases of presumptive monosomy 21 have been reported [Kaneko et al., 1975; Davis et al., 1976; Dziuba et al., 1976; Fryns et al., 1977; Garzicic et al., 1988; Gripenberg et al., 1972; Halloran et al., 1972]. Several monosomy 21 cases were reexamined for possible rearrangements and were diagnosed as unbalanced translocations [Cohen and Putnam, 1972; Holbek et al., 1974; Ikeuchi et al., 1976; Dutrillaux et al., 1973; Phelan et al., 1988; Viljoen et al., 1992; Lopez-Pajares et al., 1993].

In this report, an infant who was diagnosed as having monosomy 21 in another laboratory by routine G-banding techniques was re-evaluated by fluorescence in situ hybridization (FISH) which showed an unbalanced translocation involving 5p and 21q. A comparison of clinical and cytogenetic findings of all cases with unbalanced t(5p;21q), including our own, suggested that unbalanced t(5p;21q) occurs as a distinct syndrome which could be grouped under a new category, namely, the "5p/21q deletion syndrome."

CLINICAL REPORT

Case History

The propositus was born at 36 weeks gestation to healthy parents who are consanguineous. The family history showed one abortion at 7 weeks and a normal 5-year-old daughter. There was no history of congenital malformations or mental retardation on either side of the family. The baby was noted to have an asymmetrical face and skull, apparently low-set ears, micrognathia, hypertelorism, epicanthal folds, broad nasal bridge, high arched palate, single palmar creases, overriding toes and syndactyly of feet. He also had severe inspiratory stridor with upper airway obstruction and abnormally weak, cat like cry, hence the diagnosis of cri-du-chat syndrome was suspected. The results of chromosome analysis were reported as 45, XY, –21. The chromosomes of both parents were reported as normal.

At 6 months, the infant was referred for re-evaluation and further chromosome studies. Examination confirmed presence of the above mentioned minor anomalies, the most unusual manifestation was severe episodes of cyanotic attacks which appeared as breath-

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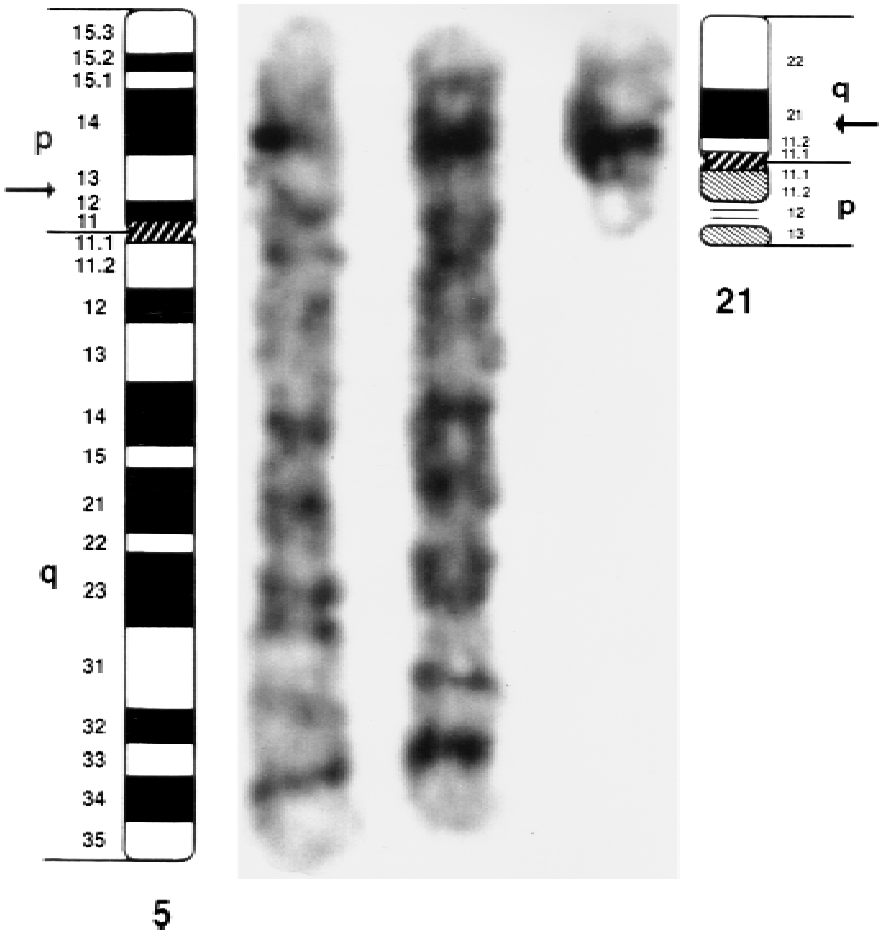


Fig. 1. Partial GTG banded karyotype of chromosome 5 and 21, showing possible translocation between the 5p and 21q. The arrows indicate breakpoints on chromosome 5 and 21.

holding spells with upper airway obstruction. The attacks became extremely severe with crying. The patient also had a very weak cry and feeding difficulties. Except for developmental delay, the infant had no other anomalies.

The patient died at home at the age of 7 months of "respiratory failure."

Cytogenetic and Fish Analysis

Phytohemagglutinin-stimulated lymphocyte cultures were analyzed by routine laboratory methods. The chromosome spreads were banded by trypsin-Giemsa banding technique. Digoxigenin-labelled coatasome 5 and 21 total chromosome probes were purchased from Oncor, Inc. (Gaithersburg, MD). FISH was performed according to the manufacturer's instructions. (Oncor coatasome starter kit, catalogue #S5200-Kit edition 2.1, January 1995.)

Briefly, 2- to 5-day-old slides with chromosome spreads were pretreated in 2× SSC solution at 37°C for 30 minutes, followed by dehydration in 70, 80, 95% ethanol for 2 minutes each. Chromosomes were then denatured in 70% formamide/2× SSC solution, pH 7.0 at 70°C for 2 minutes. The probe was also denatured at 70°C for 10 minutes and reannealed for 2 hours at 37°C. An appropriate amount of probe was then laid down on the slide for overnight hybridization at 37°C in a humidified chamber. After a rapid wash in 2× SSC, pH 7.0 solution at 72°C for 5 minutes, the detection of hybridization proceeded by applying rhodamine-labelled anti-digoxigenin and counterstaining with DAPI. The slides were scanned by a Zeiss Axiophot fluorescence microscope and pictures were taken on a 35-mm film at ASA 400 with auto-exposure.

RESULTS AND DISCUSSION

Based on 50 metaphases examined by routine GTG banding technique, a male karyotype with 45 chromosomes was found; all cells contained only one chromosome 21. However, a rearrangement between chromosomes 5 and 21 was suspected (Fig. 1) and FISH analysis was performed, confirming the existence of an unbalanced translocation between the short arm of chromosome 5 and the long arm of chromosome 21 (Figs. 2 and 3). Thus, the karyotype of the patient is correctly represented as 45,XY,der(5)t(5;21)(p13;q21),–21. A request for repeat parental chromosome analysis in our laboratory was declined. However, based on the normal chromosome findings reported in both parents of this patient, it is likely that the t(5p;21q) is a de novo event in

TABLE I. Common Clinical Findings in Cases of Unbalanced t(5p;21q) and Cri-du-Chat Syndrome*

	Present case	Phelan et al.,1988	Viljoen et al., 1992	Lopez-Pajares et al., 1993	Cri-du-chat syndrome Overhauser et al., 1994
Age[a]	6 months	11 years	16 years	15 days	
Hypertelorism	+	+	+	+	+
Epicanthal folds	+	+	–	+	+
Down slanting palpebral fissures	+	+	+	+	+
Prominent nasal bridge	+	+	+	–	+
High-arched palate	+	+	+	+	–
Abnormal ears	+	+	–	+	+
Syndactyly of toes	+	+	–	–	+/–
Palmar crease	+	+	–	–	–
Clinodactyly	–	+	–	+	+
Mental retardation	+	+	+	+	+
Developmental delay	+	+	+	+	+
Micrognathia	+	–	+	+	+
Poor cry	+	+	–	+	+
Asymmetric face	+	+	–	–	+
Microcephaly	+	+	+	–	+
Hypo/hypertonia	–	+	–	+	+
Breakpoint on 5	p13	p13/p14	p15.3	p13/p14	
Breakpoint on 21	q21	q11/q21	q22.1	q11/q21	

*A plus or minus sign indicates the presence or absence of the clinical finding.
[a]This corresponds to the age at which clinical evaluation was performed.

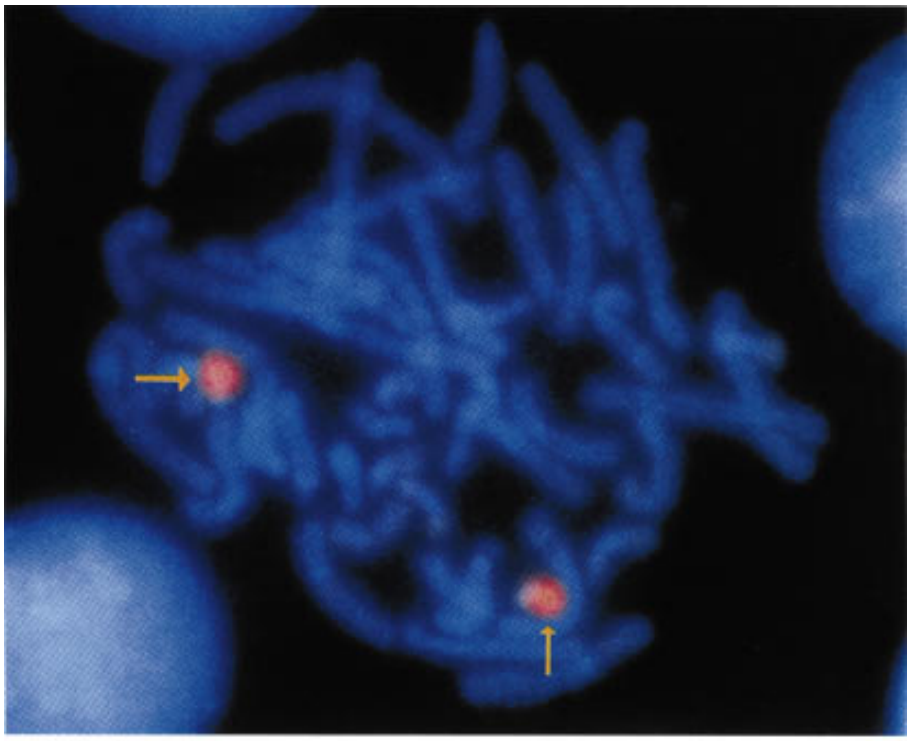
this child. Interestingly, all the previous reports of t(5p;21q) studied by molecular cytogenetic techniques were also due to a de novo event [Phelan et al., 1988; Viljoen et al., 1992; Lopez-Pajares et al., 1993; Gill et al., 1994]. The DNA probe used in the patient studied by Pellissier et al. [1987], to confirm the absence of chromosome 21 in the cells, was from the 21q22.3 region. This probe does not exclude the possibility of an unbalanced translocation involving the region proximal to 21q22.3. In the patient reported by Phelan et al. [1988] the presence of an unbalanced t(5p;21q) was demonstrated by high-resolution chromosome analysis and molecular techniques using 6 different probes from 21q. The authors also confirmed the presence of chromosome 21 material on the short arm of chromosome 5 by in situ hybridization using tritium-labeled probes. In the cases reported by Lopez-Pajares et al. [1993] and Viljoen et al. [1992] monosomy 21 was assessed as a de novo t(5p;21q) utilizing biotin-labeled chromosome 21 specific probe.

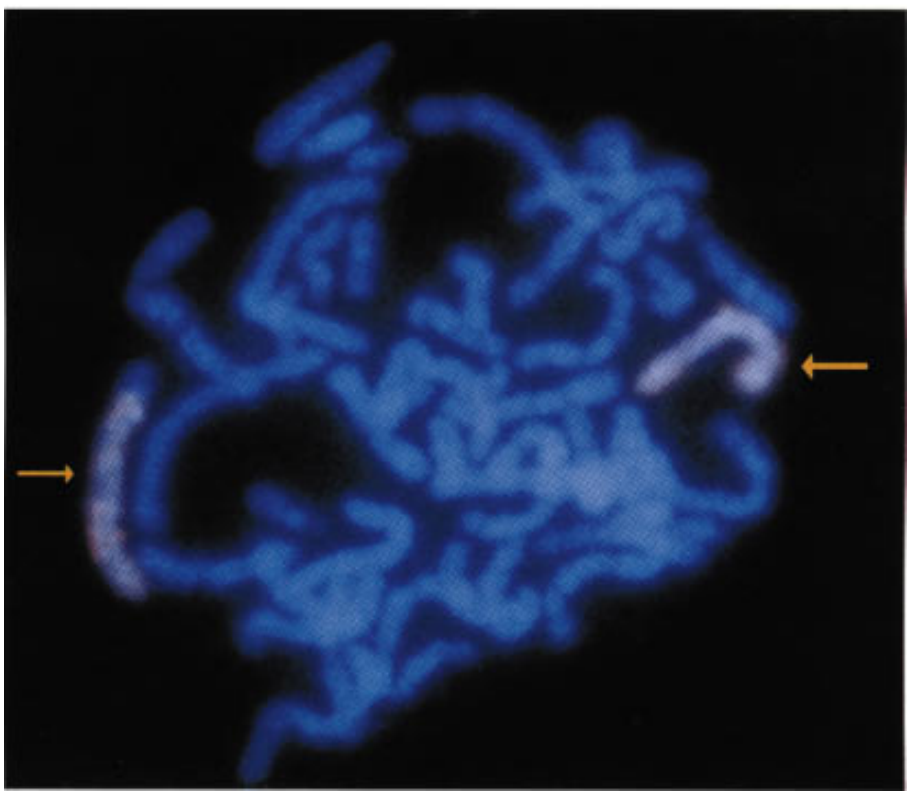
The clinical findings in all cases of t(5p;21q) reviewed in this report show a strong similarity (Table I). The breakpoint on chromosome 5 in these cases occurred in the p13–p15 region, whereas the breakpoint on chromosome 21 was in the q21–q22 region. The 5p13–p15 region encompasses the critical region for cri-du-chat syndrome [Overhauser et al., 1994]. Since the derivative chromosome 5 containing chromosomal fragments distal to 5p13 region and proximal to 21q21 region was lost in these patients, resulting in partial 5p/21q monosomy, most of the clinical findings in these cases overlapped with those of the cri-du-chat syndrome. These included mental and developmental delay, weak cry, facial asymmetry, high-arched palate, hypertelorism, microcephaly, abnormal ears, epicanthal folds and hypertonicity. The most significant finding related to cri-du-chat syndrome was the unusual weak cry in our patient and the patients reported by Phelan et al. [1988] and Lopez-Pajaras et al. [1993]. Since the typical cry in cri-du-chat patients disappears with time, it is very likely that the abnormal cry was difficult to notice in the patient reported by Viljoen et al. [1992], who had clinical evaluation at age 16 years. Interestingly, the clinical manifestations of the patient studied by Pellisier et al. [1987] also showed similarity with patients with unbalanced t(5p;21q).

Based on the reported breakpoint in t(5p;21q) cases, it appears that the amount of genetic material lost from chromosome 21 is minimal, except in the case of Viljoen et al. [1992]. Recently, Chettouh et al. [1995] constructed a molecular map of 23 manifestations seen in partial monosomy 21. The authors concluded that deletion of chromosomal regions proximal to and including a major portion of band 21q21 does not seem to produce any significant phenotypic effect in partial monosomy 21q patients. Thus, in patients with unbalanced t(5p;21q), most anomalies are likely due to partial monosomy 5p and it is not surprising that a diagnosis of cri-du-chat syndrome was suspected. However, due to the limitation of cytogenetic resolution, precise location of the breakpoint on chromosome 21 is difficult. The impact of partial monosomy 21q in patients with t(5p;21q), either due to deletion of some crucial

Fig. 2. Fluorescence in situ hybridization using chromosome 21 painting probe. The thick arrow indicates the der(5)t(5p;21q) chromosome. Note the signal on chromosome 5 is above the centromere, in the short arm.

Fig. 3. Fluorescence in situ hybridization using chromosome 5 painting probe. The thin arrow indicates the der(5)t(5p;21q) chromosome. Note the presence of chromosome 5 signal in the short arm, demonstrating that the breakpoint is most likely in the 5p13 region.





Figs. 2 and 3

genes or position effect, can only be made by further molecular analysis of the breakpoints in these patients.

Non-mosaic monosomy 21 is incompatible with life [Abeliovich et al., 1979] and reported cases of monosomy 21 were suggested to be due to unrecognized translocations resulting in partial monosomy [Schinzel, 1976, 1985]. The review of cases with unbalanced t(5p;21q) in this study supports the above assumption. We suggest that cases with unbalanced t(5p;21q) may be grouped under a new category, namely, "5p/21q deletion syndrome."

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